Journal of Diabetes Science and Technology
Volume 4, Issue 3, May 2010

ORIGINAL ARTICLES

An Analysis of the Mixing Efficiency of Neutral Protamine Hagedorn Cartridges

Scott V. Monte, Pharm.D.,[1] Patrick Comerford, Jr., Pharm.D.,[2] and Natalie Dearing, Pharm.D.[3]

Abstract

In this issue of *Journal of Diabetes Science and Technology*, Kaiser and colleagues conducted an investigation to identify variations in the delivered dose of several different isophane insulin (neutral protamine Hagedorn, NPH) brands that use glass and metal bodies ("bullets") to facilitate mixing. Using a strategy where multiple pens from each of five different NPH insulin products (Insuman Basal, sanofi-aventis, three metal bullets; Humulin N, Lilly, one glass bullet; Berlinsulin H Basal, Berlin-Chemie, one glass bullet; Insulin B. Braun Basal, two glass bullets; and Protaphane Penfill, NovoNordisk, one glass bullet) were compared at multiple sampling points and over a range of mixing procedures (3, 6, 10, and 20 times), the authors identified deviations in the delivered dose of insulin at initial use and with repeated dosing. At the initial dose, adhering with manufacturer recommendations to conduct the mixing procedure 10–20 times was found to demonstrate minimal deviation and there was no pronounced difference among the products. Decreasing the number of mixing procedures from 10–20 to 3–6 times, a more profound deviation was noted, with the Insuman Basal product demonstrating less variability in comparison to all other products evaluated. A repeated dose study (1, 2, 6, and 10) with only six mixing procedures revealed that the insulin concentration of each dose increased for all products except Insuman Basal. Clinically, numerous factors may contribute to variability observed with subcutaneous administration of isophane insulin. While data presented by Kaiser and colleagues demonstrated that the issue of proper mixing is not trivial, the modest differences observed between and within products both at the initial dose and with repeated dosing may indicate that the clinical relevance of these findings is most applicable to those requiring large doses or, alternatively, those who have otherwise unexplained hypoglycemic episodes.

J Diabetes Sci Technol 2010;4(3):658-660

Author Affiliations: [1]CPL Associates, LLC, Amherst, New York; [2]University at Buffalo School of Pharmacy and Pharmaceutical Sciences, Buffalo Medical Group, Buffalo, New York; and [3]University at Buffalo School of Pharmacy and Pharmaceutical Sciences, Lifetime Health Medical Group, West Seneca, New York

Abbreviations: (IU) international units, (NPH) neutral protamine Hagedorn, isophane insulin

Keywords: administration, insulin, isophane, mixing, pharmacodynamics, pharmacokinetics

Corresponding Author: Scott V. Monte, Pharm.D., CPL Associates, LLC, 3980 Sheridan Drive, Suite 501, Amherst, NY 14226; email address smonte@cplassociates.com

Introduction

Isophane insulin (neutral protamine Hagedorn, NPH) is a crystalline suspension of human insulin, protamine, and zinc designed to have a slower onset and a longer duration of action than that of regular human insulin. The onset of action for NPH insulin ranges from 1 to 4 hours postinjection with maximal glucose-lowering effects occurring at approximately 4–14 hours (mean 5.5 hours). The overall duration of action ranges from 10 to 24 hours.[1] In comparison to solutions of regular insulin, the absorption of NPH insulin suspension is associated with a >50% interindividual variability and a 20–40% intraindividual variability.[2,3] It has been proposed that the source of this high inter- and intra-individual variability may be due to differences in insulin dose, storage, injection technique, and injection site conditions (location, body temperature, muscle mass, and tissue vasculature).[2,4–8] In addition to these factors, an important consideration is that crystalline insulin formulations, like NPH, require adequate mixing prior to administration in order to release the insulin from self-aggregating hexamers, which form during storage.[1,3] Failure to mix the insulin suspension properly can lead to incomplete destructuration of the crystalline form and thus inaccuracies in dosing.[9,10]

Brief Study Review

In this issue of *Journal of Diabetes Science and Technology*, Kaiser and colleagues[11] conducted an investigation to identify variations in the delivered dose of several different NPH insulin brands that use glass and metal bodies ("bullets") to facilitate mixing. Using a strategy where multiple pens from each of five different NPH insulin products (Insuman Basal, sanofi-aventis, three metal bullets; Humulin N, Lilly, one glass bullet; Berlinsulin H Basal, Berlin-Chemie, one glass bullet; Insulin B. Braun Basal, two glass bullets; and Protaphane Penfill, NovoNordisk, one glass bullet) were compared at multiple sampling points and over a range of mixing procedures (3, 6, 10, and 20 times), the authors identified deviations in the delivered dose of insulin at initial use and with repeated dosing. At the initial dose, adhering with manufacturer recommendations to conduct the mixing procedure 10–20 times was found to demonstrate minimal deviation and there was no pronounced difference among the products. However, when decreasing the number of mixing procedures from 10–20 to 3–6 times, a more profound deviation was noted, with the Insuman Basal product demonstrating less variability in comparison to all other products evaluated. A repeated dose study (1, 2, 6, and 10) with only six mixing procedures revealed that the insulin concentration (units per milliliter) increased with each dose for all products except Insuman Basal. From these data, the authors concluded that pronounced differences exist among NPH products when the mixing procedure was performed only 3–6 times and that only the product with the heaviest and highest number of bullets (Insuman Basal) was mixed efficiently when only a few mixing procedures were conducted.

Clinical Implications

The inter- and intraindividual variability of the time action profile of NPH on clinical practice is significant and can be influenced by various factors. The addition of mixing bullets is the first attempt at reducing variability associated with improper mixing of NPH. While no significant difference was identified when NPH products were mixed as recommended by the manufacturer, inadequate mixing procedures can lead to deviations in the delivered dose of insulin with initial and repeated dosing.

Although the presented statistical analyses revealed the variability of Insuman Basal to be significantly less than all other products evaluated, the magnitude of effect must be considered when interpreting clinical relevance. In regard to the initial dose, the authors reported variability as the mean absolute percent deviation after selection of 28 international units (IU) for the different mixing frequencies. Calculating the actual unit difference for the respective products at only three mixing procedures (Insuman Basal, 0.308 IU; Humulin N, 0.728 IU; Berlinsulin H Basal, 1.232 IU; Insulin B. Braun Basal, 2.912 IU; and Protaphane Penfill, 1.316 IU), the range of difference between Insuman Basal and all other products for a single dose would be only 0.42–2.604 IU. Considering both the modest deviation in actual units and the time action profile, the clinical relevance of this finding is most applicable to patients requiring high doses of insulin. Evaluating the observed increase in insulin concentration with repeated dosing and only six mixing procedures, the largest magnitude of change was observed between the initial and the final dose (dose 1 vs dose 10). Insuman Basal demonstrated a minimal increase (approximately 1%), whereas all other products demonstrated an approximate 10% increase. Similar to implications of the deviations

observed with initial dosing, taking into account the time action profile, the relevance of this finding is most applicable to those on the higher end of dosing requirements or with otherwise unexplained hypoglycemia.

Moreover, the use of mixing bullets does appear to improve the consistency of the insulin dose administered to the patient when the manufacturer's recommendations to conduct the mixing procedure 10–20 times are not followed. Clinically, numerous factors may contribute to the intra- and interpatient variability observed with subcutaneous administration of isophane insulin. Data presented by Kaiser and colleagues[11] demonstrated that the issue of proper mixing is not trivial and may contribute to the observed variability. Indeed, patients that require large doses of isophane insulin or, alternatively, those who have otherwise unexplained hypoglycemic episodes may benefit from advances in mixing technologies. At the present, of the five products compared, the Insuman Basal appears to provide the least variability for initial and repeated dosing. Contrary to the author's inference that only the product with the heaviest and highest number of bullets is associated with the most efficient mixing when few mixing procedures are conducted, we believe that the design of the study is insufficient to conclude superiority of material, density, shape, or quantity of bullets. This is because the product identified to be superior was the only one to use metal and had contained more bullets than any other comparator. Moving forward, additional work should be conducted to determine the optimal characteristics and number of bullets required to optimize dosing consistency.

References:

1. Isophane insulin (NPH). Package insert. Novo Nordisk A/S DK-2880 Bagsvaerd, Denmark. Last updated: December 2005.
2. Vaag A, Handberg A, Lauritzen M, Henriksen JE, Pedersen KD, Beck-Nielsen H. Variation in absorption of NPH insulin due to intramuscular injection. Diabetes Care. 1990;13(1):74-6.
3. Heinemann L. Variability of insulin absorption and insulin action. Diabetes Technol Ther. 2002;4(5):673-82.
4. Guerci B, Sauvanet JP. Subcutaneous insulin pharmacokinetics variability and glycemic variability. Diabetes Metab. 2005;31(4 Pt 2):4S7-4S24.
5. Gin H, Hanaire-Broutin H. Reproducibility and variability in the action of injected insulin. Diabetes Metab. 2005;31(1):7-13.
6. Koivisto VA, Felig P. Alterations in insulin absorption and in blood glucose control associated with varying insulin injection sites in diabetic patients. Ann Intern Med. 1980;92(1):59-61.
7. Binder C, Lauritzen T, Faber O, Pramming S. Insulin pharmacokinetics. Diabetes Care. 1984;7(2):188-99.
8. Lauritzen T, Pramming S, Gale E, Deckert T, Binder C. Absorption of isophane (NPH) insulin and its clinical implications. Br Med J (Clin Res Ed). 1982;285(6336):159-62.
9. Jehle PM, Micheler C, Jehle DR, Breitig D, Boehm BO. Inadequate suspension of neutral protamine Hagendorn (NPH) insulin in pens. Lancet. 1999;354(9190):1604-7.
10. Lepore M, Bartocci L, Fanelli C, Pampanelli S, Porcellati F, Bolli GB. Effect of adequate vs inadequate resuspension of NPH insulin prior to s.c. injection on pharmacokinetics and -dynamics in T1DM. Diabetes. 2001;44 (Suppl. 1):A25 [abstract OP92].
11. Kaiser P, Maxeiner S, Weise A, Nolden F, Borck A, Forst T, Pfützner A. Assessment of the mixing efficiency of neutral protamine hagedorn cartridges. J Diabetes Sci Technol. 2010;4(3):652-7.